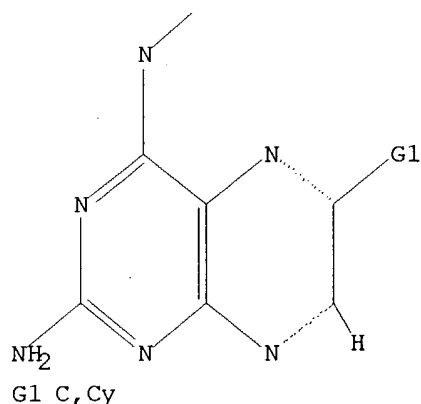


10/070976



Structure attributes must be viewed using STN Express query preparation.

=> s l6 sss full

FULL SEARCH INITIATED 19:05:01 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 869 TO ITERATE

100.0% PROCESSED 869 ITERATIONS
SEARCH TIME: 00.00.01

42 ANSWERS

L7 42 SEA SSS FUL L6

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
155.42	615.05

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	-20.79

CA SUBSCRIBER PRICE

FILE 'CAPLUS' ENTERED AT 19:05:06 ON 06 MAY 2004

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 6 May 2004 VOL 140 ISS 19

FILE LAST UPDATED: 5 May 2004 (20040505/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

10/070976

=> s 17

L8 10 L7

=> d 18 1-10 ibib abs hitstr

L8 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:392358 CAPLUS

DOCUMENT NUMBER: 137:119060

TITLE: Structural Requirements for Inhibition of the Neuronal Nitric Oxide Synthase (NOS-I): 3D-QSAR Analysis of 4-Oxo- and 4-Amino-Pteridine-Based Inhibitors

AUTHOR(S): Matter, Hans; Kotsonis, Peter; Klingler, Otmar; Strobel, Hartmut; Froehlich, Lothar G.; Frey, Armin; Pfleiderer, Wolfgang; Schmidt, Harald H. H. W.

CORPORATE SOURCE: Molecular Modeling, Aventis Pharma, Frankfurt am Main, 65926, Germany

SOURCE: Journal of Medicinal Chemistry (2002), 45(14), 2923-2941

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The family of homodimeric nitric oxide synthases (NOS I-III) catalyzes the generation of the cellular messenger nitric oxide (NO) by oxidation of the substrate L-arginine. The rational design of specific NOS inhibitors is of therapeutic interest in regulating pathol. NO levels associated with sepsis, inflammatory, and neurodegenerative diseases. The cofactor (6R)-5,6,7,8-tetrahydrobiopterin (H4Bip) maximally activates all NOSs and stabilizes enzyme quaternary structure by promoting and stabilizing dimerization. Here, we describe the synthesis and three-dimensional (3D) quant. structure-activity relationship (QSAR) anal. of 65 novel 4-amino- and 4-oxo-pteridines (antipterins) as inhibitors targeting the H4Bip binding site of the neuronal NOS isoform (NOS-I). The exptl. binding modes for two inhibitors complexed with the related endothelial NO synthase (NOS-III) reveal requirements of biol. affinity and form the basis for ligand alignment. Different alignment rules were derived by building other compds. accordingly using manual superposition or a genetic algorithm for flexible superposition. Those alignments led to 3D-QSAR models (comparative mol. field anal. (CoMFA) and comparative mol. similarity index anal. (CoMSIA)), which were validated using leave-one-out cross-validation, multiple analyses with two and five randomly chosen cross-validation groups, perturbation of biol. activities by randomization or progressive scrambling, and external prediction. An iterative realignment procedure based on rigid field fit was used to improve the consistency of the resulting partial least squares models. This led to consistent and highly predictive 3D-QSAR models with good correlation coeffs. for both CoMFA and CoMSIA, which correspond to exptl. determined NOS-II and -III H4Bip binding site topologies as well as to the NOS-I homol. model binding site in terms of steric, electrostatic, and hydrophobic complementarity. These models provide clear guidelines and accurate activity predictions for novel NOS-I inhibitors.

IT 278800-01-4P 330575-46-7P 330575-47-8P
330575-48-9P

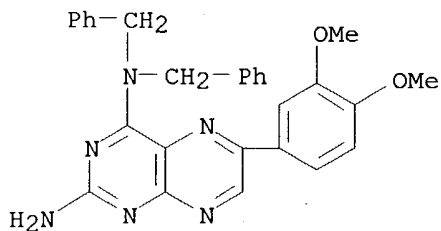
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and QSAR of 4-oxo- and 4-amino-pteridine-based neuronal NOS inhibitors)

RN 278800-01-4 CAPLUS

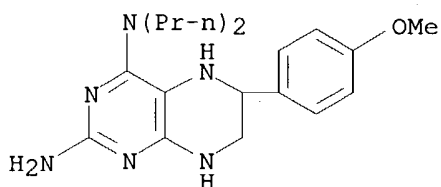
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CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-bis(phenylmethyl)-
(9CI) (CA INDEX NAME)



RN 330575-46-7 CAPLUS

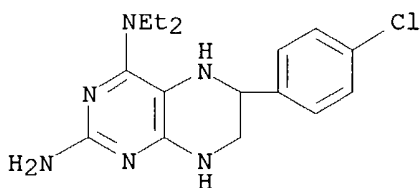
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RN 330575-47-8 CAPLUS

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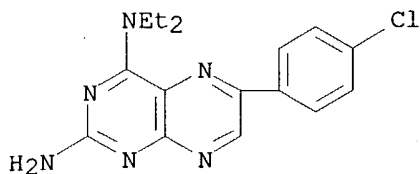


● 2 HCl

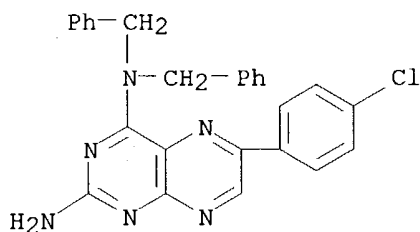
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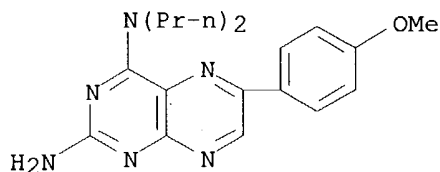
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RN 278800-00-3 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4,N4-bis(phenylmethyl)- (9CI)
(CA INDEX NAME)



RN 278800-04-7 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L8 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:228889 CAPLUS
DOCUMENT NUMBER: 134:237499
TITLE: Preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for use as pharmaceuticals
INVENTOR(S): Pfleiderer, Wolfgang; Schmidt, Harald; Froehlich, Lothar; Kotsonis, Peter; Taghavi-Moghadam, Shahriyar
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021619	A1	20010329	WO 2000-EP8833	20000911

present case

10/070976

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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EP 1216246 A1 20020626 EP 2000-964154 20000911

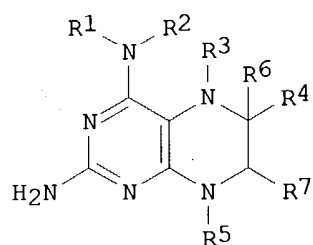
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PRIORITY APPLN. INFO.: DE 1999-19944767 A 19990917

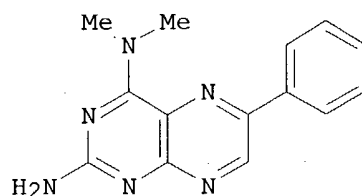
WO 2000-EP8833 W 20000911

OTHER SOURCE(S): MARPAT 134:237499

GI



I.



II

AB Pteridines, such as I [R1, R2 = H, alkyl, aryl, arylalkyl; R1R2 = nitrogen bound heterocyclyl, such as 1-piperidiny1 or 4-morpholinyl; R4 = alkyl, alkenyl, alkynyl, cycloalkenyl, aryl, etc.; R3, R5 = acyl, aroyl, R6 = R7 = H, or R3R6 = R5R7 = bond;], were prepared for pharmaceutical use. Thus, pteridine II was prepared via cyclocondensation of N4,N4-dimethylpyrimidinetetramine dihydrochloride and phenylglyoxal monoxime. The prepared pteridines were tested for nitric oxide synthase inhibiting activity.

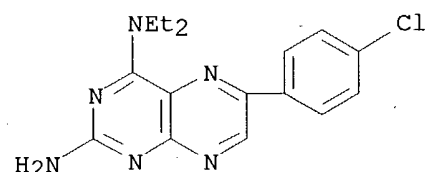
IT 278799-98-7P 278800-02-5P 278800-04-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for pharmaceutical use)

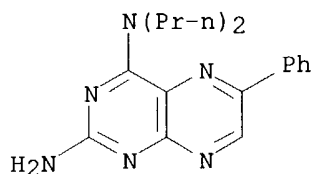
RN 278799-98-7 CAPLUS

CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4,N4-diethyl- (9CI) (CA INDEX NAME)

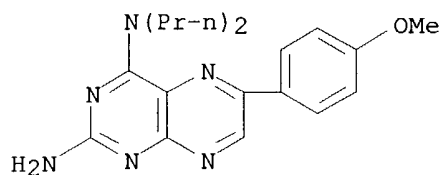


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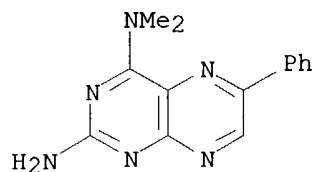
RN 278800-04-7 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



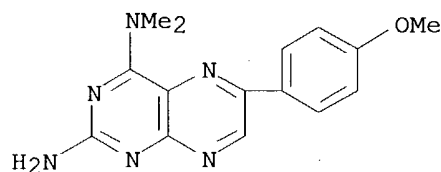
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278799-96-5P 278799-99-8P 278800-00-3P
278800-01-4P 278800-03-6P 278800-05-8P
330575-31-0P 330575-45-6P 330575-46-7P
330575-47-8P 330575-48-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for pharmaceutical use)

RN 247913-51-5 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-phenyl- (9CI) (CA INDEX NAME)

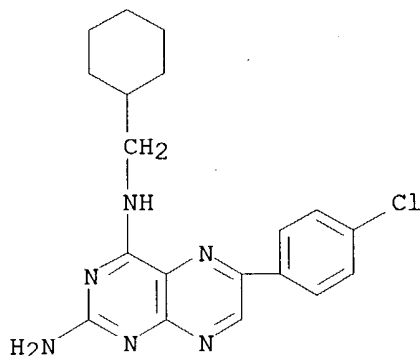


RN 247913-52-6 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



10/070976

CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4-(cyclohexylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:457070 CAPLUS
DOCUMENT NUMBER: 133:73895
TITLE: Preparation of pteridine derivatives for pharmaceutical use in the treatment of inflammatory diseases and autoimmune disorders

INVENTOR(S): Waer, Mark Joseph Albert; Herdewijn, Piet Andre
Maurits Maria; Pflleiderer, Wolfgang Eugen

PATENT ASSIGNEE(S): K.U. Leuven Research & Development, Belg.

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

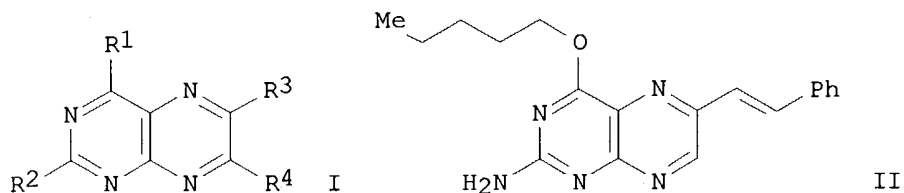
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039129	A1	20000706	WO 1999-EP10320	19991228
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JP 2002533464	T2	20021008	JP 2000-591040	19991228
US 2004077859	A1	20040422	US 2003-651604	20030829
PRIORITY APPLN. INFO.: US 1998-113989P P 19981228 60/117,989				
WO 1999-EP10320 W 19991228				
US 2001-869468 B2 20011010				
OTHER SOURCE(S): MARPAT 133:73895 09/269,468 ABN				

Schmidt
Frohlich
Kotsan
Machmann

60/117,989

10/651,601

GI



AB Pteridines, such as I [R1, R2 = NH2, NHOH, alkylamine, dialkylamine, alkyloxyamine, dialkyloxyamine, nitrogen containing heterocyclyl, etc.; R3 = halogen, alkoxy, alkyl, aryl, etc.; R4 = H, alkyl, alkoxy, aryl] were prepared for pharmaceutical use in the treatment of inflammatory diseases and autoimmune disorders. Thus, pteridine II was prepared in 72% yield by reaction of 6-chloro-4-(pentyloxy)-2-pteridinamine and styrene using palladium acetate, tri-*o*-tolylphosphine, cuprous iodide, and triethylamine in acetonitrile. The prepared pteridines were tested for immunosuppressive and anti-inflammatory activity.

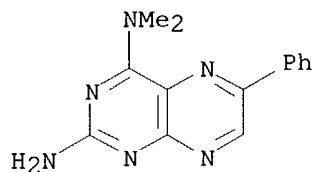
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 278800-21-8P 278800-22-9P 278800-24-1P
 278800-26-3P 278800-27-4P 278800-29-6P
 278800-30-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pteridine derivs. for pharmaceutical use in the treatment of inflammatory diseases and autoimmune disorders)

RN 247913-51-5 CAPLUS

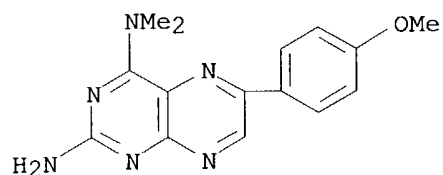
CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-phenyl- (9CI) (CA INDEX NAME)



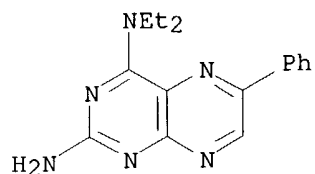
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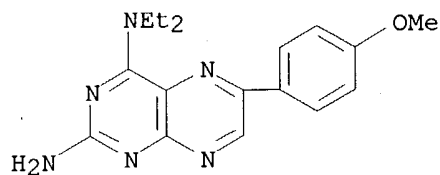
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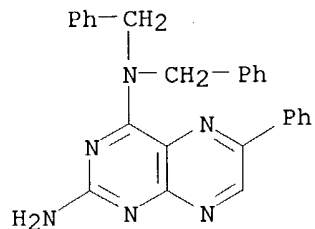
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CN 2,4-Pteridinediamine, N4,N4-diethyl-6-phenyl- (9CI) (CA INDEX NAME)



RN 247913-55-9 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-diethyl-6-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)

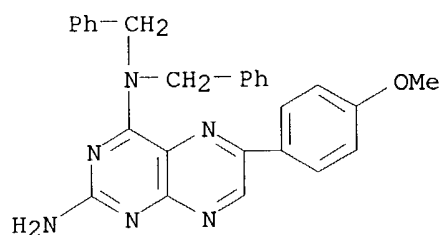


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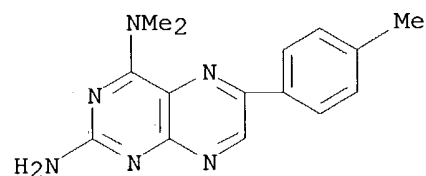


RN 247913-57-1 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)

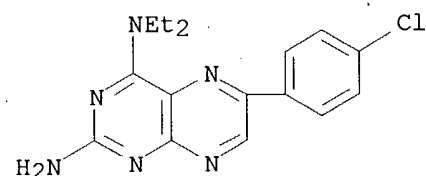
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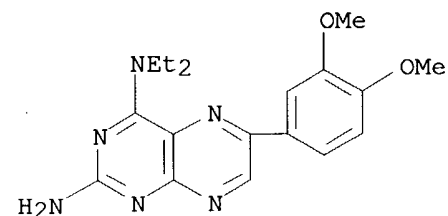
RN 278799-96-5 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-(4-methylphenyl)- (9CI) (CA INDEX NAME)



RN 278799-98-7 CAPLUS
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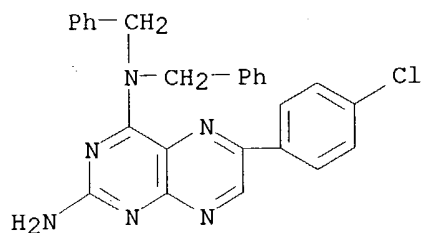


RN 278799-99-8 CAPLUS
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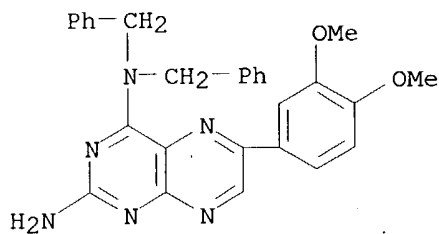


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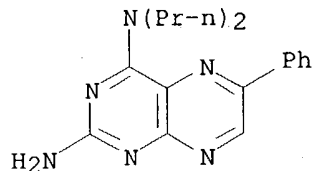
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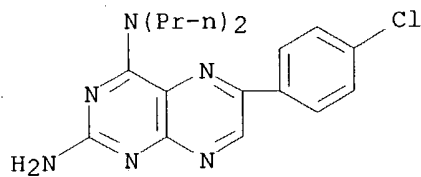
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RN 278800-02-5 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4,N4-dipropyl- (9CI) (CA INDEX NAME)

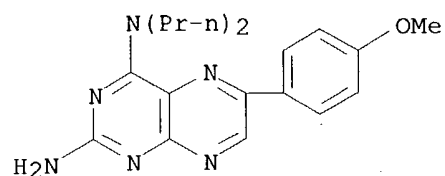


RN 278800-03-6 CAPLUS
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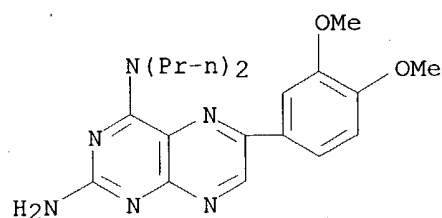
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10/070976



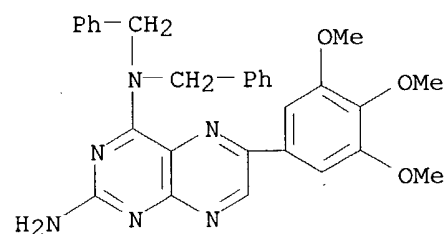
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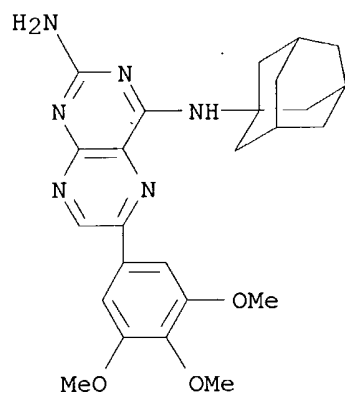
RN 278800-17-2 CAPLUS

CN 2,4-Pteridinediamine, N4,N4-bis(phenylmethyl)-6-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



RN 278800-19-4 CAPLUS

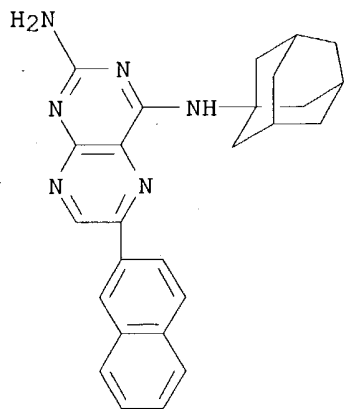
CN 2,4-Pteridinediamine, N4-tricyclo[3.3.1.3^7]dec-1-yl-6-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



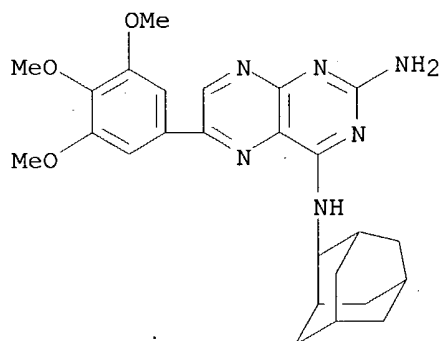
RN 278800-20-7 CAPLUS

10/070976

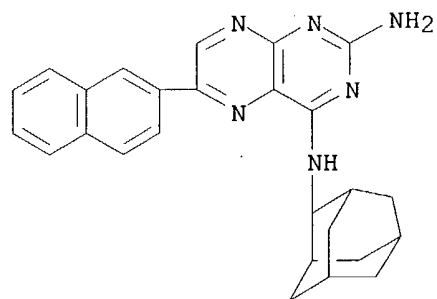
CN 2,4-Pteridinediamine, 6-(2-naphthalenyl)-N4-tricyclo[3.3.1.1^{3,7}]dec-1-yl-
(9CI) (CA INDEX NAME)



RN 278800-21-8 CAPLUS
CN 2,4-Pteridinediamine, N4-tricyclo[3.3.1.1^{3,7}]dec-2-yl-6-(3,4,5-
trimethoxyphenyl)- (9CI) (CA INDEX NAME)

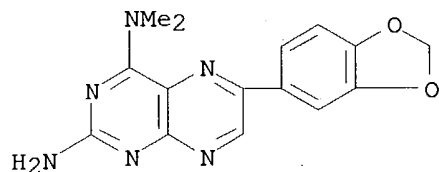


RN 278800-22-9 CAPLUS
CN 2,4-Pteridinediamine, 6-(2-naphthalenyl)-N4-tricyclo[3.3.1.1^{3,7}]dec-2-yl-
(9CI) (CA INDEX NAME)

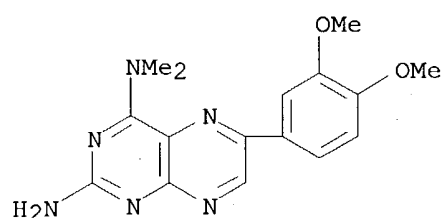


RN 278800-24-1 CAPLUS
CN 2,4-Pteridinediamine, 6-(1,3-benzodioxol-5-yl)-N4,N4-dimethyl- (9CI) (CA
INDEX NAME)

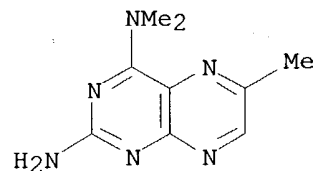
10/070976



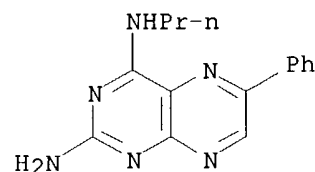
RN 278800-26-3 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



RN 278800-27-4 CAPLUS
CN 2,4-Pteridinediamine, N4,N4,6-trimethyl- (9CI) (CA INDEX NAME)

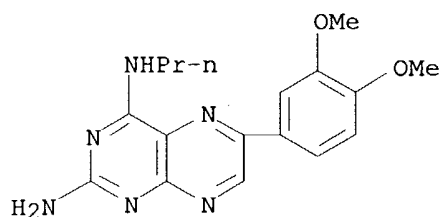


RN 278800-29-6 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4-propyl- (9CI) (CA INDEX NAME)



RN 278800-30-9 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4-propyl- (9CI) (CA INDEX NAME)

10/070976



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:766098 CAPLUS

DOCUMENT NUMBER: 132:93157

TITLE: Pteridines CX. Synthesis and properties of 6-substituted 2,4-diaminopteridines and pterins

AUTHOR(S): Traub, Hermann; Pfleiderer, Wolfgang

CORPORATE SOURCE: Fakultat Fur Chemie, Universitat Konstanz, Konstanz, D-78432, Germany

SOURCE: Pteridines (1999), 10(3), 79-90

CODEN: PTRDEO; ISSN: 0933-4807

PUBLISHER: International Society of Pteridinology

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 132:93157

AB A series of 6-substituted 2,4-diaminopteridines and pterins were synthesized by nucleophilic displacement reactions at the side chain of 6-bromomethyl-2,4-diaminopteridine and 6-bromomethylpterin using various types of O-, N- and S-nucleophiles.

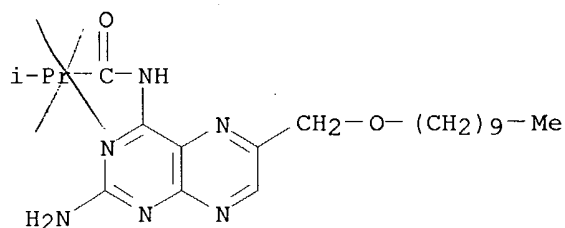
IT 254755-84-5P 254755-85-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of 6-substituted 2,4-diaminopteridines and pterins via nucleophilic substitution reactions)

RN 254755-84-5 CAPLUS

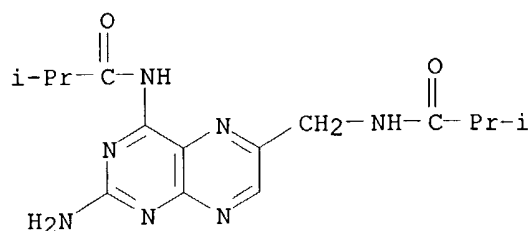
CN Propanamide, N-[2-amino-6-[(decyloxy)methyl]-4-pteridinyl]-2-methyl- (9CI) (CA INDEX NAME)



RN 254755-85-6 CAPLUS

CN Propanamide, N-[2-amino-6-[[2-methyl-1-oxopropyl]amino]methyl]-4-pteridinyl]-2-methyl- (9CI) (CA INDEX NAME)

10/070976

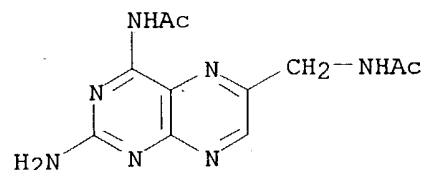


IT 254755-86-7P

RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of 6-substituted 2,4-diaminopteridines and pterins via nucleophilic substitution reactions)

RN 254755-86-7 CAPLUS

CN Acetamide, N-[[4-(acetylamino)-2-amino-6-pteridinyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:589097 CAPLUS

DOCUMENT NUMBER: 131:317316

TITLE: Inhibition of Neuronal Nitric Oxide Synthase by
4-Amino Pteridine Derivatives: Structure-Activity
Relationship of Antagonists of (6R)-5,6,7,8-
Tetrahydrobiopterin Cofactor

AUTHOR(S): Froehlich, Lothar G.; Kotsonis, Peter; Traub, Hermann;
Taghavi-Moghadam, Shahriyar; Al-Masoudi, Najim;
Hofmann, Heinrich; Strobel, Hartmut; Matter, Hans;
Pfleiderer, Wolfgang; Schmidt, Harald H. H. W.

CORPORATE SOURCE: Department of Pharmacology and Toxicology,
Julius-Maximilians University Wuerzburg, Wuerzburg,
97078, Germany

SOURCE: Journal of Medicinal Chemistry (1999), 42(20),
4108-4121

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The family of nitric oxide synthases (NOS) catalyzes the conversion of L-arginine to L-citrulline and nitric oxide (NO), an important cellular messenger mol. which has been implicated in the pathophysiol. of septic shock and inflammatory and neurodegenerative disease states. NOS can be maximally activated by the ubiquitous cofactor, (6R)-5,6,7,8-tetrahydrobiopterin (H4Bip), and antagonists of H4Bip may be of therapeutic importance to inhibit pathol. high NO formation. The 4-amino substituted analog of H4Bip was reported to be a potent NOS inhibitor. Therefore, we developed a series of novel 4-amino pteridine derivs., anti-pterins, to pharmacol. target the neuronal isoform of nitric oxide

synthase (NOS-I). To functionally characterize the pterin/anti-pterin interaction and establish a structure-activity relationship (SAR), we systematically altered the substituents in the 2-, 4-, 5-, 6-, and 7-position of the pteridine nucleus. Varying the substitution pattern in the 2-, 5-, and 7-position resulted in no significant inhibitory effect on enzyme activity. In contrast, bulky substituents in the 6-position, such as Ph, markedly increased the inhibitory potency of the reduced 4-amino-5,6,7,8-tetrahydropteridines, possibly as a consequence of hydrophobic interactions within NOS-I. However, this was not the case for the aromatic 4-amino pteridines. Interestingly, chemical modification of the 4-amino substituent by dialkyl/diaralkylation together with 6-arylation of the aromatic 2,4-diamino pteridine resulted in potent and efficacious inhibitors of NOS-I, suggesting possible hydrophilic and hydrophobic interactions within NOS-I. This SAR agrees with (a) the recently published crystal structure of the oxygenase domain of the inducible NOS isoform (NOS-II) and (b) the comparative mol. field anal. of selected NOS-I inhibitors, which resulted in a 3D-QSAR model of the pterin binding site interactions. Further optimization should be possible when the full length structure of NOS-I becomes available.

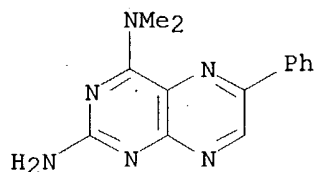
IT 247913-51-5P 247913-52-6P 247913-54-8P
247913-55-9P 247913-56-0P 247913-57-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis of and inhibition of neuronal nitric oxide synthase by aminopteridines)

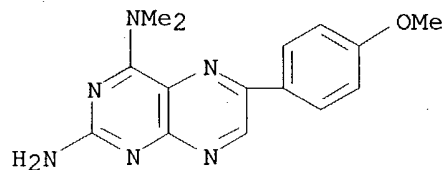
RN 247913-51-5 CAPLUS

CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-phenyl- (9CI) (CA INDEX NAME)



RN 247913-52-6 CAPLUS

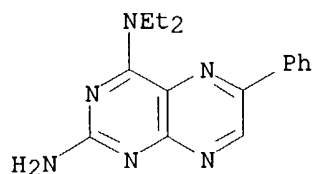
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



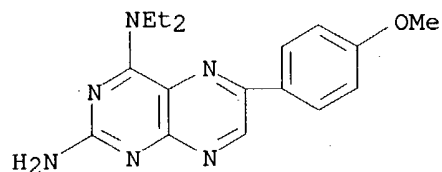
RN 247913-54-8 CAPLUS

CN 2,4-Pteridinediamine, N4,N4-diethyl-6-phenyl- (9CI) (CA INDEX NAME)

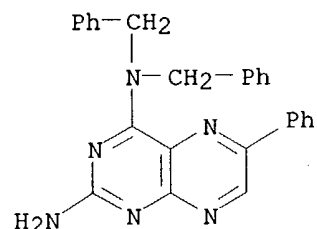
10/070976



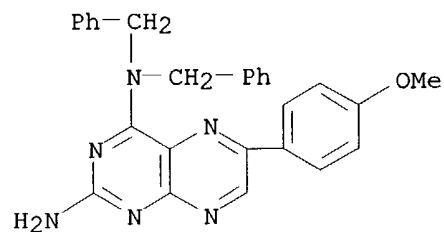
RN 247913-55-9 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-diethyl-6-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 247913-56-0 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 247913-57-1 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:7345 CAPLUS
DOCUMENT NUMBER: 118:7345
TITLE: Synthesis and properties of N-(α -aminoacyl) derivatives of methotrexate
AUTHOR(S): Cheung, H. T. A.; Dong, Z.; Smal, M.; Tattersall, M.

10/070976

CORPORATE SOURCE:
SOURCE:

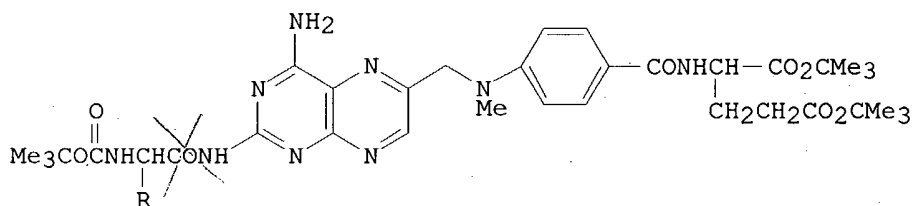
H. N.

Dep. Pharm., Univ. Sydney, Sydney, 2006, Australia
Pteridines (1992), 3(1-2), 101-2

CODEN: PTRDEO; ISSN: 0933-4807

DOCUMENT TYPE:
LANGUAGE:
GI

Journal
English



AB Methotrexate was converted to its di-tert-Bu ester which coupled with Boc- α -amino acids (leucine, isoleucine, norleucine) to give the 2-(N-Boc- α -aminoacyl) derivs. I (R = CH₂CHMe₂, CHMeEt, n-Bu) along with the 4-(N-Boc- α -aminoacyl) and 2,4-di(N-Boc- α -aminoacyl) derivs. I were treated with F₃CCO₂H to give the corresponding deprotected 2- α -aminoacylmethotrexates in quant. yields.

IT 125507-12-2P 144864-86-8P 144864-87-9P

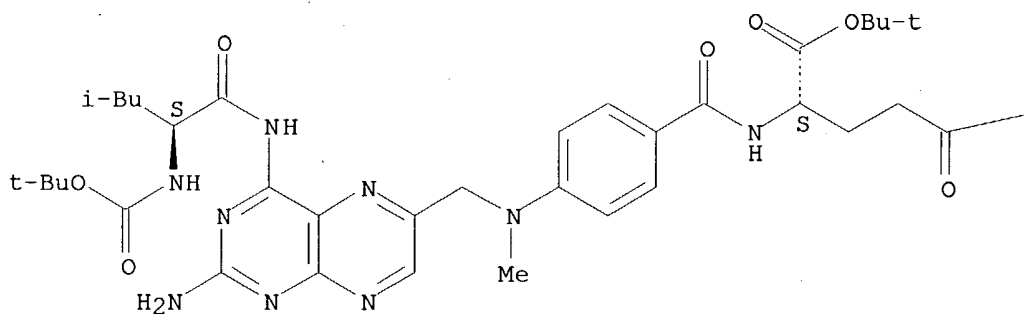
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 125507-12-2 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



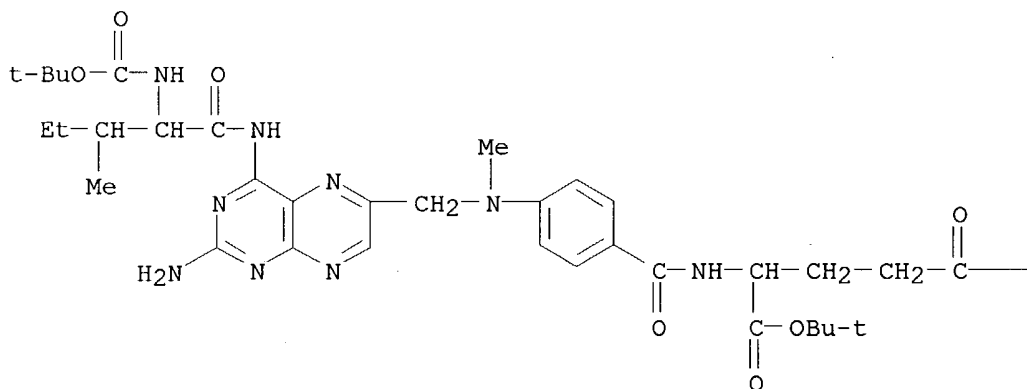
—OBU-t

RN 144864-86-8 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[[(1,1-

dimethylethoxy) carbonyl] amino]-3-methyl-1-oxopentyl] amino]-6-
pteridiny]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester,
[S-(R*,R*)]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

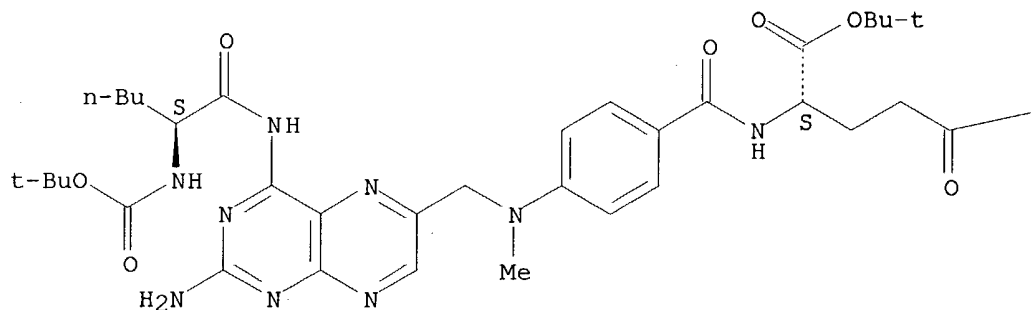
—OBu-t

RN 144864-87-9 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[[(1,1-
dimethylethoxy) carbonyl] amino]-1-oxohexyl] amino]-6-
pteridiny]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester,
(S)- (9CI) (CA INDEX NAME)

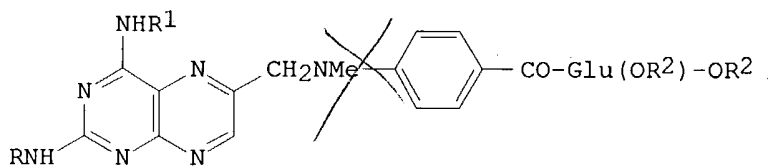
Absolute stereochemistry.

PAGE 1-A



—OBu-t

L8 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1990:99224 CAPLUS
 DOCUMENT NUMBER: 112:99224
 TITLE: N-(L- α -aminoacyl) derivatives of methotrexate
 AUTHOR(S): Cheung, H. T. Andrew; Boadle, Deborah K.; Tran, Trung Q.
 CORPORATE SOURCE: Dep. Pharm., Univ. Sydney, Sydney, Australia
 SOURCE: Heterocycles (1989), 28(2), 751-8
 CODEN: HTCYAM; ISSN: 0385-5414
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 112:99224
 GI



AB Coupling of methotrexate ester I (R = R1 = H, R2 = CMe3) with alanine and leucine derivs. gave aminoacyl analogs I (R, R1 = Boc-Leu, Boc-Ala; R2 = CMe3; Boc = Me3CO2C). The positions of the aminoacyl groups were determined by ¹³C NMR. Hydrolysis of I (R = Boc-Ala, Boc-Leu; R1 = H, R2 = Me3C) gave methotrexate analogs I (R = H-Ala, H-Leu; R1 = R2 = H) (II), but the other aminoacyl analogs gave decomposition products. Enzymic cleavage of II gave methotrexate.

IT 125507-12-2P 125507-13-3P

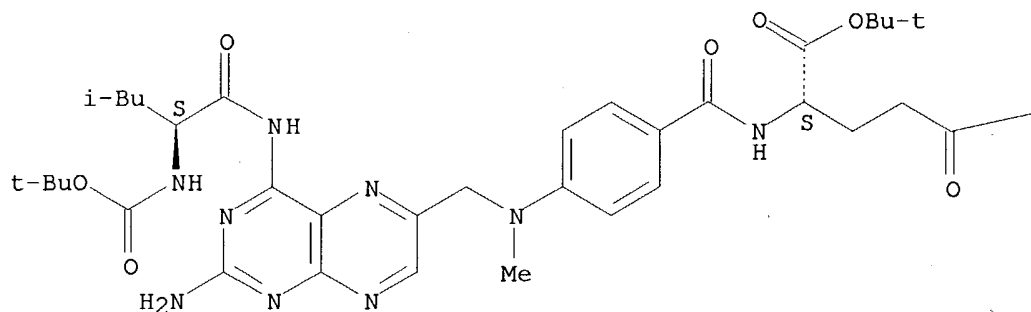
RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation, attempted deblocking, and carbon-13 NMR of)

RN 125507-12-2 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[[1,1-dimethylethoxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester,
 (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



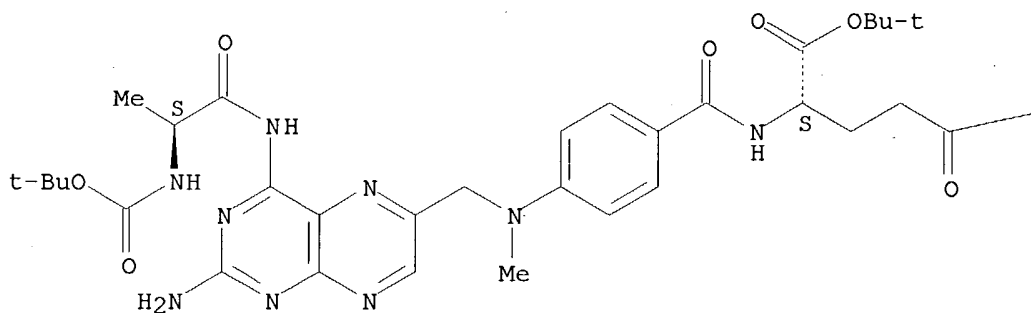
PAGE 1-B

—OBu-t

RN 125507-13-3 CAPLUS
 CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[1,1-dimethylethoxy)carbonyl]amino]-1-oxopropyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



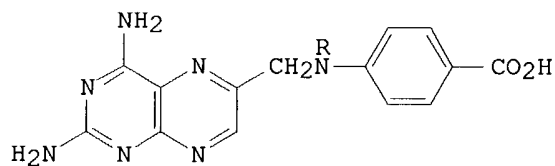
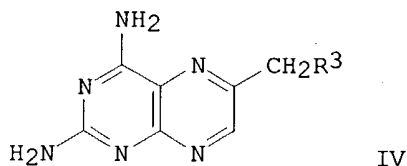
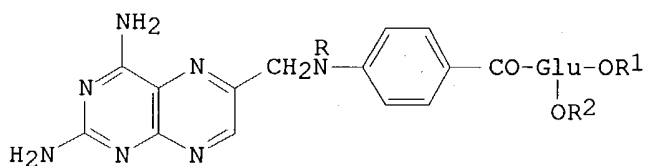
PAGE 1-B

—OBu-t

L8 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1985:167139 CAPLUS
 DOCUMENT NUMBER: 102:167139
 TITLE: Methotrexate analogs. 25. Chemical and biological studies on the γ -tert-butyl esters of methotrexate and aminopterin
 AUTHOR(S): Rosowsky, Andre; Freisheim, James H.; Bader, Henry;

10/070976

Forsch, Ronald A.; Susten, Sandra A.; Cucchi, Carol A.; Frei, Emil, III
CORPORATE SOURCE: Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Journal of Medicinal Chemistry (1985), 28(5), 660-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 102:167139
GI



AB γ -tert-Bu aminopterin (I; R = R1 = H, R2 = CMe3) (II) was prepared, and new routes to the known γ -tert-Bu methotrexate (I; R = Me, R1 = H, R2 = CMe3) (III) were developed. Thus, pteridine IV (R3 = OH) was brominated by Br2/PPh3 to give IV (R3 = Br), which was treated in situ with p-H2NC6H4CO2H to give pterioic acid V (R = H), which was formylated to give V (R = CHO). The latter was condensed with H-Glu(OCMe3)-OMe.HCl by ClCO2CH2CHMe2 in DMF containing Et3N to give I (R = CHO, R1 = Me, R2 = CMe3), which was hydrolyzed and then deformylated to give II. II was also prepared by treating IV.HBr (R3 = Br) with p-RNHC6H4CO-Glu(OCMe3)-OR1 (VI, R = R1 = H) in AcNMe2 containing Me2CHNEt2. III was prepared by brominating IV (R3 = OH), treating the resulting IV (R3 = Br) with VI (R = R1 = Me), and hydrolyzing the resulting I (R = R1 Me, R2 = CMe3). The inhibitory effects of II on the activity of dihydrofolate reductase (DHFR) from L1210 murine leukemia cells, the growth of 4210 cells and CEM human leukemic lymphoblasts in suspension culture, and the growth of human squamous cell carcinoma of the head and neck in monolayer culture were compared with the effects of III and the parent acids aminopterin (I, R-R2 = H) and methotrexate (I, R = Me, R1 = R2 = H). The activity of II was close to that of III in the DHFR inhibition assay, but II was more potent than III against cells in culture and against L1210 leukemia in mice.

IT 95485-11-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

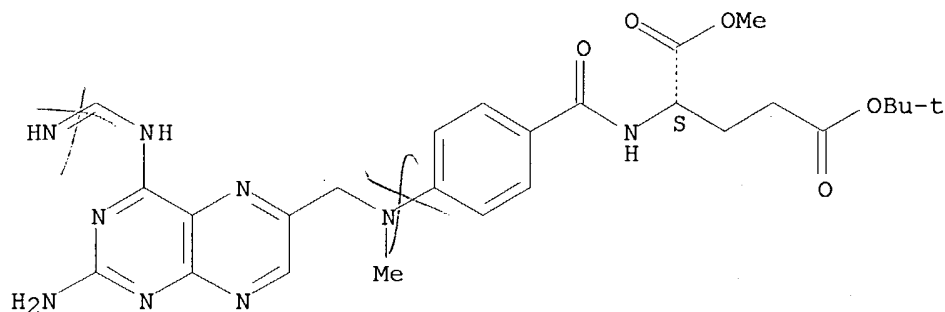
10/070976

(preparation and hydrolysis of)

RN 95485-11-3 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-[(iminomethyl)amino]-6-pteridinyl)methyl]methylamino]benzoyl]-, 5-(1,1-dimethylethyl) 1-methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



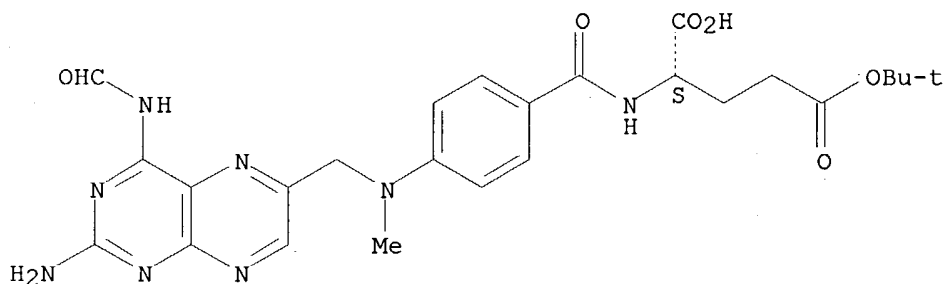
IT 95485-13-5P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 95485-13-5 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-(formylamino)-6-pteridinyl)methyl]methylamino]benzoyl]-, 5-(1,1-dimethylethyl) ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1961:28447 CAPLUS

DOCUMENT NUMBER: 55:28447

ORIGINAL REFERENCE NO.: 55:5650f-g

TITLE: A simple method for the demonstration of antimetabolites

AUTHOR(S): Pershin, G. N.; Shcherbakova, L. I.

CORPORATE SOURCE: S. Ordzhonikidze All-Union Sci.-Research Chemo-Pharm. Inst., Moscow

SOURCE: Biokhimiya (Moscow) (1960), 25, 684-7

CODEN: BIOHAO; ISSN: 0320-9725

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

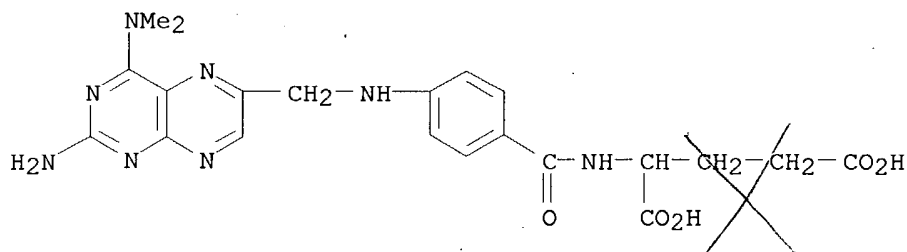
AB Antimetabolites, such as 6-mercaptapurine, 2-amino-6-mercaptapurine and 8-azaguanine, which interfered with purine metabolism, arrested the growth of Escherichia coli; antimetabolite activity was counteracted by

hypoxanthine, adenine, and guanine. Among the other substances normally used in arresting malignant growths, aminopterin, 4-dimethylaminopteroylglutamic acid, and embichin also arrested E. coli growth. Purine bases had no effect on these substances. Colchamine and thiophosphoramidate (thioteph) arrested the growth of E. coli in high concns. only; Myleran was ineffective.

IT **103508-85-6**, Glutamic acid, N-{p-[[(2-amino-4-dimethylamino-6-pteridiny]methyl]amino)benzoyl]-
(effect on Escherichia coli)

RN 103508-85-6 CAPLUS

CN Glutamic acid, N-[p-[[(2-amino-4-dimethylamino-6-pteridiny]methyl]amino]benzoyl]- (6CI) (CA INDEX NAME)



L8 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1961:9549 CAPLUS

DOCUMENT NUMBER: 55:9549

ORIGINAL REFERENCE NO.: 55:1909c

TITLE: Evaluation of antileukemic agents employing advanced leukemia L1210 in mice. III. Congeners of folic acid

AUTHOR(S): Venditti, John M.; Humphreys, Stewart R.; Mantel, Nathan; Kline, Ira; Goldin, Abraham

CORPORATE SOURCE: Natl. Cancer Inst., Bethesda, MD

SOURCE: Cancer Research (1960), 20(No. 10;Pt. 2), 698-733

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IT **97115-74-7**, Glutamic acid, N-{p-[[(2-amino-4-dimethylamino-6-pteridiny]methyl]methylamino)benzoyl]-
(as neoplasm inhibitor)

RN 97115-74-7 CAPLUS

CN Glutamic acid, N-[p-[[[(2-amino-4-(dimethylamino)-6-pteridiny]methyl]methylamino]benzoyl]- (6CI, 7CI) (CA INDEX NAME)

